

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>REP06088W0</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/GB 00/ 01198</b>	International filing date (day/month/year) <b>29/03/2000</b>	(Earliest) Priority Date (day/month/year) <b>31/03/1999</b>
Applicant  <b>CHIROTECH TECHNOLOGY LIMITED</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

### 1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**BIOCATALYST AND ITS USE IN ENZYMATIC RESOLUTION OF RACEMIC BETA-LACTAMS**

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/01198

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D205/12 C12P41/00 C12N1/20 //(C12N1/20,C12R1:38)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C12P C12N C12R

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 424 064 A (ENZYMATIX LTD.) 24 April 1991 (1991-04-24) claims 1,12-18 ---	1, 10, 15, 16
A,P	WO 99 41405 A (G. D. SEARLE & CO.) 19 August 1999 (1999-08-19) abstract page 2, line 8 - line 14 page 3, line 13 - line 17 ---	1, 15, 16
A	P. CSOMOS ET AL.: TETRAHEDRON: ASYMMETRY, vol. 7, no. 6, 1996, pages 1789-96, XP004047667 cited in the application page 1789, abstract; page 1794-5, paragraph "Experimental" --- -/--	1, 10-16



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

29 June 2000

Date of mailing of the international search report

19/07/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
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Authorized officer

Hass, C

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/01198

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	L. T. KANERVA ET AL.: TETRAHEDRON: ASYMMETRY, vol. 7, no. 6, 1996, pages 1705-16, XP004047657 cited in the application page 1705, abstract page 1711 -page 1716 ----	1,10-16
A	WO 97 10713 A (CIBA-GEIGY AG) 27 March 1997 (1997-03-27) cited in the application page 2, line 23 - line 26; claim 18 ----	1,11-14
A	WO 92 18477 A (CHIRO LTD.) 29 October 1992 (1992-10-29) cited in the application claims 1,2; example 1 ----	1,11-14
A	EP 0 232 017 A (THE UPJOHN CO.) 12 August 1987 (1987-08-12) cited in the application page 7, line 60 -page 8, line 1; claim 1 ----	1,11-14
A	GB 1 273 278 A (FARBWERKE HOECHST AG) 3 May 1972 (1972-05-03) cited in the application claims 1,11,12,16 ----	1,11,12
A	M. KURIHARA ET AL.: TETRAHEDRON LETTERS, vol. 26, no. 47, 1985, pages 5831-4, XP002141492 cited in the application ----	
A	N. TAMURA ET AL.: TETRAHEDRON LETTERS, vol. 27, no. 32, 1986, pages 3749-52, XP002141493 cited in the application ----	
A	EP 0 002 564 A (BEECHAM GROUP LTD) 27 June 1979 (1979-06-27) cited in the application page 25, line 1 - line 6 -----	

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/01198

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 424064	A	24-04-1991	AT 118208 T	15-02-1995
			DE 69016739 D	23-03-1995
			DE 69016739 T	14-06-1995
			DK 424064 T	26-06-1995
			ES 2067693 T	01-04-1995
			GR 3015887 T	31-07-1995
			JP 2648013 B	27-08-1997
			JP 3218380 A	25-09-1991
			US 5284769 A	08-02-1994
			US 5498625 A	12-03-1996
			US 5688933 A	18-11-1997
WO 9941405	A	19-08-1999	AU 2758899 A	30-08-1999
WO 9710713	A	27-03-1997	AU 6988996 A	09-04-1997
WO 9218477	A	29-10-1992	AU 1669792 A	17-11-1992
EP 232017	A	12-08-1987	AU 6849687 A	14-08-1987
			EP 0282492 A	21-09-1988
			JP 1501470 T	25-05-1989
			WO 8704429 A	30-07-1987
GB 1273278	A	03-05-1972	BE 741422 A	08-05-1970
			DE 1807495 A	11-06-1970
			FR 2022807 A	07-08-1970
			NL 6916439 A	11-05-1970
EP 2564	A	27-06-1979	DE 2862419 D	26-07-1984
			JP 54076593 A	19-06-1979
			US 4289696 A	15-09-1981
			US 4347181 A	31-08-1982
			US 4223038 A	16-09-1980

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C A WOLFE

Accounts A J SHIAFKOU Computer Systems G G AMABILINO  
Records: Trade Marks N D STANTON Patents G M ALDERMAN

5/10  
492  
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34 Chemin des Colombettes  
1211 Geneva 20  
SWITZERLAND

REC'D 17 JUL 2000

WIPO PCT

BY FACSIMILE  
CONFIRMATION BY POST

12th July 2000

**CONFIRMATION**

Dear Sirs

**International Patent Application No. PCT/GB00/01198**  
**Chirotech Technology Limited**  
**Our Ref: REP06088WO**

The invention in this Application relates, *inter alia*, to biological material. Two deposits of biological material have been made, and the name and address of the depository institution and the dates of deposit, have been provided. The first accession number has also been provided in the specification as filed; the second accession number is 41042.

The Applicants intend to insert "41042" in the blanks at page 6 line 26 and in claims 15 and 16.

I take this opportunity of requesting confirmation that the priority document has been received. I have had no official notification to this effect, and I should appreciate having your advice by return fax.

Yours faithfully  
GILL JENNINGS & EVERY

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W8  
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S HALEY      L A SAMUELS

M V GORDON

A L MACQUARRIE  
A J SMITH

C A WOLFE

Accounts A J SHIAFKOU      Computer Systems G G AMABILINO  
Records: Trade Marks N D STANTON      Patents G M ALDERMAN

The International Bureau of WIPO  
34 Chemin des Colombettes  
1211 Geneva 20  
SWITZERLAND

REC'D 04 SEP 2000

WIPO

PCT

30th August 2000

**AMENDMENT UNDER ARTICLE 19 PCT**

Dear Sirs

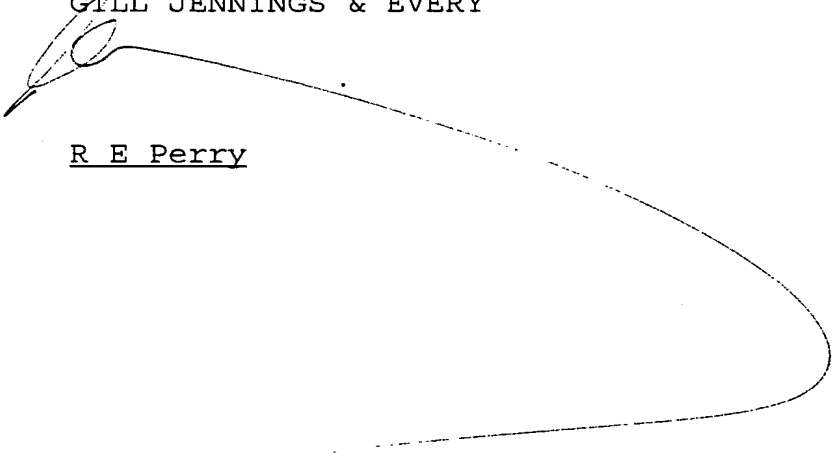
International Patent Application No. PCT/GB00/01198  
Chirotech Technology Limited, et al  
Our Ref: REP06088WO

A new page 12 is filed herewith in triplicate. Claims 10, 15 and 16 have been amended.

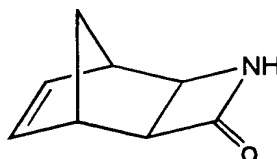
Statement under Article 19(1)

Claims 10, 15 and 16 have been amended, in order to give the accession number (not available on filing) and the correct taxonomic name for the deposited strain. In support of these amendments, I refer to my letter dated 12th July and also to the attached copies of a Declaration and receipt issued by NCIMB.

Yours faithfully  
GILL JENNINGS & EVERY

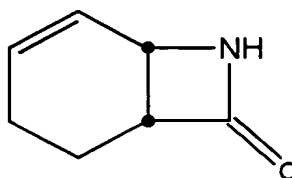
  
R E Perry

8. A process according to claim 7, wherein the lactam is 3-azatricyclo[4.2.1.0<sup>2,5</sup>]non-7-en-4-one (2)



(2)

9. A process according to claim 1, wherein the lactam is 7-azabicyclo[4.2.0]oct-4-en-8-one (3)



(3)

- 10.(amended) A process according to any preceding claim, wherein the lactamase enzyme is obtainable from a microorganism having the characteristics of that available as the *Rhodococcus globerulus* strain identified as CMC103381, Accession No. NCIMB 41042.

11. Enantiomerically enriched 3-azatricyclo[4.2.1.0<sup>2,5</sup>]non-7-en-4-one of formula (2) as shown in claim 8, in an enantiomeric excess of at least 80%.

12. Enantiomerically enriched 7-azabicyclo[4.2.0]oct-4-en-8-one of formula (3) as shown in claim 9, in an enantiomeric excess of at least 80%.

13. A lactam according to claim 11 or claim 12, wherein the enantiomeric excess is at least 95%.

14. Enantiomerically enriched levorotatory enantiomer according to any of claims 11 to 13.

- 15.(amended) A lactamase enzyme obtainable from a microorganism having the characteristics of that available as the *Rhodococcus globerulus* strain identified as CMC103381, Accession No. NCIMB 41042.

- 16.(amended) *Rhodococcus globerulus* strain identified as CMC103381, Accession No. NCIMB 41042.


**BUDAPEST TREATY ON THE INTERNATIONAL  
RECOGNITION OF THE DEPOSIT OF MICROORGANISMS  
FOR THE PURPOSES OF PATENT PROCEDURE**

Chirotech Technology Ltd  
Cambridge Science Park  
Milton Road  
Cambridge  
CB4 0WG

**INTERNATIONAL FORM**

**RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT**  
issued pursuant to Rule 7.1 by the  
**INTERNATIONAL DEPOSITARY AUTHORITY**  
identified at the bottom of this page

NAME AND ADDRESS OF DEPOSITOR

<b>I. IDENTIFICATION OF THE MICROORGANISM</b>	
Identification reference given by the DEPOSITOR:  <i>Rhodococcus globerulus</i> CMC 103381	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY:  NCIMB 41042
<b>II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION</b>	
The microorganism identified under I above was accompanied by:  <div style="display: flex; align-items: flex-start;"><div style="margin-right: 10px;"><input type="checkbox"/>  <input checked="" type="checkbox"/></div><div><div>a scientific description</div><div>a proposed taxonomic designation</div></div></div> (Mark with a cross where applicable)	
<b>III. RECEIPT AND ACCEPTANCE</b>	
This International Depositary Authority accepts the microorganism identified under I above, which was received by it on 29 March 2000 (date of the original deposit) <sup>1</sup>	
<b>IV. RECEIPT OF REQUEST FOR CONVERSION</b>	
The microorganism identified under I above was received by this International Depositary Authority on (date of the original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion)	
<b>V. INTERNATIONAL DEPOSITARY AUTHORITY</b>	
Name: NCIMB Ltd.,  Address: 23 St Machar Drive Aberdeen AB24 3RY Scotland, UK.	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorised official(s):   Date: 25 August 2000

<sup>1</sup> Where Rule 6/4(d) applies, such date is the date on which the status of International Depositary Authority was acquired.  
Form BP/4 (sole page)



FOR THE PURPOSES OF PATENT PROCEDURE

Chirotech Technology Ltd  
Cambridge Science Park  
Milton Road  
Cambridge  
CB4 0WG

INTERNATIONAL FORM

**VIABILITY STATEMENT**  
issued pursuant to Rule 10.2 by the  
INTERNATIONAL DEPOSITARY AUTHORITY  
identified on the following page

NAME AND ADDRESS OF THE PARTY  
TO WHOM THE VIABILITY STATEMENT  
IS ISSUED

<b>I. DEPOSITOR</b>	<b>II. IDENTIFICATION OF THE MICROORGANISM</b>
Name: AS ABOVE Address:	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: NCIMB 41042 Date of the deposit or of the transfer <sup>1</sup> : 29 March 2000
<b>III. VIABILITY STATEMENT</b>	
The viability of the microorganism identified under II above was tested on 30 March 2000 <sup>2</sup> . On that date, the said microorganism was:  <div style="display: flex; align-items: center;"><div style="margin-right: 10px;"><div style="text-align: center;"><sup>3</sup> X</div><div style="text-align: center;"><input checked="" type="checkbox"/></div></div><div>3 viable</div></div> <div style="display: flex; align-items: center;"><div style="margin-right: 10px;"><div style="text-align: center;"><input type="checkbox"/></div></div><div>no longer viable</div></div>	

<sup>1</sup> Indicate the date of the original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).

<sup>2</sup> In the cases referred to in Rule 10.2(a)(ii) and (iii), refer to the most recent viability test.

<sup>3</sup> Mark with a cross the applicable box.

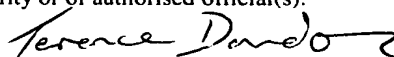
IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED<sup>4</sup>

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: NCIMB Ltd.,

Address: 23 St Machar Drive  
Aberdeen  
AB24 3RY  
Scotland

Signature(s) of person(s) having the power  
to represent the International Depositary  
Authority or of authorised official(s):



Date: 25 August 2000

<sup>4</sup> Fill in if the information has been requested and if the results of the test were negative.

PCT

REC'D 05 APR 2001

WIPO

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference REP06088WO	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/01198	International filing date (day/month/year) 29/03/2000	Priority date (day/month/year) 31/03/1999
International Patent Classification (IPC) or national classification and IPC C07D205/12		
Applicant CHIROTECH TECHNOLOGY LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  25/08/2000	Date of completion of this report  03.04.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Gregoire, A  Telephone No. +49 89 2399 2994  

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01198

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-10 as originally filed

**Claims, No.:**

1-7 as originally filed

8-16 as received on 31/08/2000 with letter of 30/08/2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01198

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

## II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:  
**see separate sheet**

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. Statement

Novelty (N)	Yes:	Claims	5, 7-11, 15-16
	No:	Claims	1-4, 6, 12-14
Inventive step (IS)	Yes:	Claims	8-9
	No:	Claims	1-7, 10-16
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations  
**see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/GB00/01198

**Re Item I**

**Basis of the opinion**

The amended Claims 8-16 can not be taken into account for the establishment of this opinion since a different microorganism (*Rhodococcus globerulus* instead of *Pseudomonas putida*) as well as **different accession numbers** (NCIMB 41042 instead of NCIMB 41013) than those originally filed (see p. 6 l. 26) are mentioned. This does not comply with Art. 34-2-b) PCT. The CMC number mentioned by the applicant can not be taken as evidence of the same microorganism since it is a reference given by said applicant.

**Re Item II**

**Priority**

Since the prior document is not available for the time being, the priority of the present application is considered valid and will be checked later if necessary.

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1) Reference is made to the following documents :**

- D1: EP-A-0 424 064 (ENZYMATIX LTD.) 24 April 1991 (1991-04-24)
- D2: WO 99 41405 A (G. D. SEARLE & CO.) 19 August 1999 (1999-08-19)
- D3: WO 97 10713 A (CIBA-GEIGY AG) 27 March 1997 (1997-03-27) cited in the application
- D4: WO 92 18477 A (CHIROs LTD.) 29 October 1992 (1992-10-29) cited in the application
- D5: EP-A-0 232 017 (THE UPJOHN CO.) 12 August 1987 (1987-08-12) cited in the application
- D6: GB-A-1 273 278 (FARBWERKE HOECHST AG) 3 May 1972 (1972-05-03) cited in the application
- D7: EP-A-0 002 564 (BEECHAM GROUP LTD) 27 June 1979 (1979-06-27) cited in the application

- D8: P. CSOMOS ET AL.: TETRAHEDRON: ASYMMETRY, vol. 7, no. 6, 1996, pages 1789-96, XP004047667 cited in the application
- D9: L. T. KANERVA ET AL.: TETRAHEDRON: ASYMMETRY, vol. 7, no. 6, 1996, pages 1705-16, XP004047657 cited in the application
- D10: M. KURIHARA ET AL.: TETRAHEDRON LETTERS, vol. 26, no. 47, 1985, pages 5831-4, XP002141492 cited in the application
- D11: N. TAMURA ET AL.: TETRAHEDRON LETTERS, vol. 27, no. 32, 1986, pages 3749-52, XP002141493 cited in the application

**2) Novelty (Art. 33 (1) and (2) PCT) :**

The technical features of Claims 1-4 and 6 are not appropriate to establish novelty over D4. This document indeed discloses an enzymatic resolution process of  $\beta$ -lactam falling in the scope of the above mentioned claims. The applicant states that the lactimase of D4 does not react with the lactones mentioned in claim 1 but does not prove it. No relevant information can indeed be found neither in the mentioned prior art nor in the original disclosure, the latter only indicating a higher activity of the strain claimed than that observed in D4 (p. 4 line 28-30).

Claim 5 is new since no further use of the amino-acid formed during the enzymatic hydrolysis for the  $\beta$ -lactams synthesis is reported. Specific  $\beta$ -lactam are disclosed in Claims 7-9 for use in the process as mentioned in Claim 1 which were not employed before, rendering the said claims novel.

*pseudomonas putida* strain is not reported in the prior art, Claim 10 is thus new. The compound disclosed in Claim 11 is new. This is not the case of that of Claim 12 which has been specifically disclosed in D3 (example H1.1 p. 12). D3 states p. 2 l. 23-26 that the invention embraces all possible isomers in pure form or in the form of a mixture. Claims 12-14 are consequently not considered as novel.

Claims 15 and 16 are new since they relate to an unknown enzyme.

**3) Inventive Step (Art. 33 (1) and (3) PCT) :**

The technical problem underlying the present application is the provision of a new process for the preparation of enantiomerically enriched  $\beta$ -lactam.

Enantioselective hydrolysis of closely related compounds have been reported in the prior art, e. g.  $\beta$ -lactam in D4 or  $\gamma$ -lactam in D1, using enzymes such as

*rhodococcus* or *pseudomonas*. The question arises if this enzyme can really hydrolyse selectively any  $\beta$ -lactams as defined in Claims 1, 6 and 7. Since the prior art is focused on specific  $\beta$ -lactams and enzymatic enantioselectivity can vary significantly with slight changes such as the nature of the reaction, it is not scientifically reasonable that an enantiomer of any  $\beta$ -lactam could be separated in a significant yield using the biocatalytic process of the present invention. Claims 8 and 9 disclose specific  $\beta$ -lactams that the enzyme of the present invention can hydrolyse unexpectedly fast compared to what is disclosed in the prior art. Inventive step can therefore be acknowledged for these claims. Except for claims 8 and 9, the application does not comply with Art. 33 (3) PCT.

**Re Item VIII**

**Certain observations on the international application**

- 1) Claim 1 does not meet the requirement of Art. 6 PCT. The definition of the enzyme suitable for the present invention is given through the result to be achieved. The description is not considered to give sufficient guidance so as to allow the skilled person to identify with a reasonable chance of success a suitable enzyme for the process claimed without undue burden of experimentation. The scope of lactamase enzymes available as claimed is much broader than the one of the specific enzyme exemplified in the description (Art. 5 and 6 PCT).
- 2) The deposition of the strains ensures that the requirements of Art. 5 PCT regarding sufficiency of disclosure of the invention at the priority date are met. In the absence of a deposit receipt or equivalent proof of the deposit of the strain whose NCIMB number is 41013 (Rule 13bis PCT), the requirements of Art. 5 PCT are not considered to be met.
- 3) The use of functional definition like "non-interfering groups" is not allowable since it is not clear which group are meant (Art. 6 and Guidelines III-6.5 PCT).



## PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
United States Patent and Trademark Office  
Box PCT  
Washington, D.C. 20231  
ETATS-UNIS D'AMERIQUE

COMMUNICATION IN CASES FOR WHICH  
NO OTHER FORM IS APPLICABLE

Date of mailing (day/month/year) 04 October 2000 (04.10.00)	
Applicant's or agent's file reference REP06088WO	<b>REPLY DUE</b> see paragraph 1 below
International application No. PCT/GB00/01198	International filing date (day/month/year) 29 March 2000 (29.03.00)
Applicant CHIROTECH TECHNOLOGY LIMITED	

1. ☐ REPLY DUE within \_\_\_\_\_ months/days from the above date of mailing☐ NO REPLY DUE, however, see below☒ IMPORTANT COMMUNICATION☐ INFORMATION ONLY

2. COMMUNICATION:

Please find attached for your consideration, copy of a letter form the agent of record (received via fax at the International Bureau on 12 July 2000), concerning deposits of biological material.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer Maria Victoria CORTIELLO Telephone No. (41-22) 338.83.38
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## P. ENT COOPERATION TREATY

**PCT****NOTIFICATION CONCERNING  
AMENDMENTS OF THE CLAIMS****(PCT Rule 62 and  
Administrative Instructions, Section 417)**

From the INTERNATIONAL BUREAU

To:

Mrs I. Diallo  
European Patent Office  
Erhardtstrasse 27  
D-80331 Munich  
ALLEMAGNE

in its capacity as International Preliminary Examining Authority

Date of mailing (day/month/year)

28 November 2000 (28.11.00)

International application No.

PCT/GB00/01198

International filing date (day/month/year)

29 March 2000 (29.03.00)

Applicant

CHIROTECH TECHNOLOGY LIMITED et al

The International Bureau hereby transmits a copy of the amendments to the claims under Article 19 together with any accompanying statement (Rule 62).

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

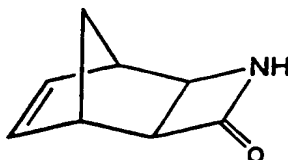
Facsimile No. (41-22) 740.14.35

Authorized officer

Pascal Piriou

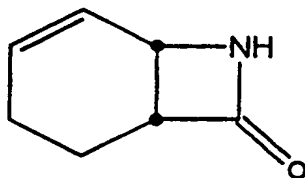
Telephone No. (41-22) 338.83.38

8. A process according to claim 7, wherein the lactam is 3-azatricyclo[4.2.1.0<sup>2,5</sup>]non-7-en-4-one (2)



(2)

9. A process according to claim 1, wherein the lactam is 7-azabicyclo[4.2.0]oct-4-en-8-one (3)



(3)

10. A process according to any preceding claim, wherein the lactamase enzyme is obtainable from a microorganism having the characteristics of that available as the *Pseudomonas putida* strain identified as CMC103381, Accession No. NCIMB .....

11. Enantiomerically enriched 3-azatricyclo[4.2.1.0<sup>2,5</sup>]non-7-en-4-one of formula (2) as shown in claim 8, in an enantiomeric excess of at least 80%.

12. Enantiomerically enriched 7-azabicyclo[4.2.0]oct-4-en-8-one of formula (3) as shown in claim 9, in an enantiomeric excess of at least 80%.

13. A lactam according to claim 11 or claim 12, wherein the enantiomeric excess is at least 95%.

14. Enantiomerically enriched levorotatory enantiomer according to any of claims 11 to 13.

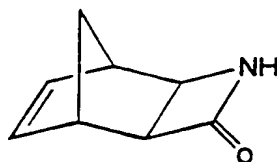
15. A lactamase enzyme obtainable from a microorganism having the characteristics of that available as the *Pseudomonas putida* strain identified as CMC103381, Accession No. NCIMB .....

16. *Pseudomonas putida* strain identified as CMC103381, Accession No. NCIMB .....

## AMENDED CLAIMS

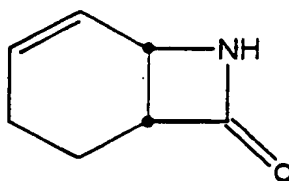
[received by the International Bureau on 4 September 2000 (04.09.00); original claims 10, 15 and 16 amended; remaining claims unchanged (1 page)]

8. A process according to claim 7, wherein the lactam is 3-azatricyclo[4.2.1.0<sup>2,5</sup>]non-7-en-4-one (2)



(2)

9. A process according to claim 1, wherein the lactam is 7-azabicyclo[4.2.0]oct-4-en-8-one (3)



(3)

10.(amended) A process according to any preceding claim, wherein the lactamase enzyme is obtainable from a microorganism having the characteristics of that available as the *Rhodococcus globerulus* strain identified as CMC103381, Accession No. NCIMB 41042.

11. Enantiomerically enriched 3-azatricyclo[4.2.1.0<sup>2,5</sup>]non-7-en-4-one of formula (2) as shown in claim 8, in an enantiomeric excess of at least 80%.

12. Enantiomerically enriched 7-azabicyclo[4.2.0]oct-4-en-8-one of formula (3) as shown in claim 9, in an enantiomeric excess of at least 80%.

13. A lactam according to claim 11 or claim 12, wherein the enantiomeric excess is at least 95%.

14. Enantiomerically enriched levorotatory enantiomer according to any of claims 11 to 13.

15.(amended) A lactamase enzyme obtainable from a microorganism having the characteristics of that available as the *Rhodococcus globerulus* strain identified as CMC103381, Accession No. NCIMB 41042.

16.(amended) *Rhodococcus globerulus* strain identified as CMC103381, Accession No. NCIMB 41042.

Statement under Article 19(1)

Claims 10, 15 and 16 have been amended, in order to give the accession number (not available on filing) and the correct taxonomic name for the deposited strain. In support of these amendments, I refer to my letter dated 12th July and also to the attached copies of a Declaration and receipt issued by NCIMB.